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Synthesis of the Aromatic and Monosaccharide Moieties of Staurosporine[1,2]

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Efficient synthetic routes have been developed for the heteroaromatic unit **4** and some aminohexoses similar to **5**, which are structural fragments of staurosporine (**1**). Aromatic lactone **4** has been prepared in four steps from 3,4-dibromomaleimide in good overall yield. A strategy utilizing Diels–Alder [4 + 2] cycloadditions of benzyl sulfinylcarbamate was used to synthesize staurosporine amino sugars in both the pyranose form **37** and in acyclic versions **38**, **41**, and **42**. A novel feature of the work involved stereospecific syn epoxidations of the 3,6-dihydrothiazine oxide adducts **15** and **16** directed by the sulfinyl oxygen.

Staurosporine (**1**) was first isolated from a culture of *Streptomyces staurosporeus* in 1977.[3a] Its molecular structure, which was established by X-ray crystallography a year later,[3b,c] is composed of a hexacyclic heteroaromatic system and an aminohexose joined by a unique bis-N-glycosidic linkage. More recently, structurally related metabolites such as K252a (**2**)[4] and rebeccamycin (**3**)[5] have been isolated from other microorganisms. In addition, Steglich et al.[6] discovered several years ago that the slime mold *Acyria denudata* produces a series of pigments very closely related to the polycyclic aromatic aglycons of **1**–**3**. Staurosporine is of interest both because of its fascinating structural array and its hypotensive and antimicrobial activity.[3] Moreover, several compounds in this group of metabolites are potent inhibitors of protein kinase C,[7] and some show antitumor activity.[5]

Several research groups have recently published routes leading to the aromatic framework of these natural products.[1,7-10] In this paper are described the details of our synthetic studies on the heteroaromatic system **4** and the amino sugar component of staurosporine. As discussed below, we have stereospecifically prepared the aminohexose moiety both in a cyclic pyranose form similar to **5a** and as protected acyclic keto aldehyde derivatives related to **5b** using a strategy based upon *N*-sulfinyl Diels–Alder [4 + 2] cycloadditions.[11]

Our synthesis of the aromatic fragment **4** utilized a variation of the efficient methodology developed by Steglich[6] for the slime mold pigments (Scheme I). 3,4-Dibromomaleimide (**6**) was N-benzylated to afford **7**, which upon treatment with indolemagnesium bromide yielded diindolylmaleimide **8**. After some experimentation, it was found that oxidative cyclization of **8** to hexacyclic imide **9** could be effected in high yield with a mixture of *p*-toluenesulfonic acid and DDQ in refluxing benzene. Several attempts were made to reduce imide **9** to lactam **4** with lithium aluminum hydride and related metal hydrides. Unfortunately, only partial reduction to the hydroxy lactam occurred, even under forcing conditions.[2] However, compound **9** could be reduced successfully to the desired lactam **4** via the Clemmensen reduction conditions used by Hughes and Raphael in their synthesis of the staurosporine aromatic unit.[9,12]

In recent years we have described applications of *N*-sulfinyl dienophile [4 + 2] cycloadditions to the syntheses

(1) For a preliminary account of a portion of this work, see: Weinreb, S.M.; Garigipati, R. S.; Gainor, J. A. *Heterocycles* **1984**, *21*, 309.

(2) Taken from the Ph.D. Theses of J. A. Gainor (1983) and R. P. Joyce (1986), The Pennsylvania State University.

(3) (a) Omura, S.; Iwai, Y.; Nakayawa, A.; Awaya, J.; Tsuchiya, T.; Takahashi, Y.; Masuma, R. *J. Antibiot.* **1977**, *30*, 275. (b) Furusaki, A.; Hashiba, N.; Matsumoto, T. *J. Chem. Soc., Chem. Commun.* **1978**, 800. (c) Furusaki, A.; Hashiba, N.; Matsumoto, T.; Hirano, A.; Iwai, Y.; Omura, S. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3681.

(4) Sezaki, M.; Sasaki, T.; Nakazawa, T.; Takeda, U.; Iwata, M.; Watanabe, T.; Koyama, M.; Kai, F.; Shomura, T.; Kojima, M. *J. Antibiot.* **1985**, *10*, 1437. Yasuzawa, T.; Iida, T.; Yoshida, M.; Hirayama, N.; Takahashi, M.; Shirahata, K.; Sano, H. *J. Antibiot.* **1986**, *11*, 1072.

(5) (a) Nettleton, D. E.; Doyle, T. W.; Krishnan, B.; Matsumoto, G. K.; Clardy, J. *Tetrahedron Lett.* **1985**, *26*, 4011. (b) Kaneko, T.; Wong, H.; Okamoto, K. T.; Clardy, J. *Tetrahedron Lett.* **1985**, *26*, 4015.

(6) Steglich, W.; Steffan, B.; Kopanski, L.; Eckhardt, G. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 459.

(7) Kase, H.; Iwahashi, K.; Matsuda, Y. *J. Antibiot.* **1986**, *11*, 1059. Nakanishi, S.; Matsuda, Y.; Iwahashi, K.; Kase, H. *J. Antibiot.* **1986**, *11*, 1066. Tamaoki, T.; Nomoto, H.; Takahashi, I.; Kato, Y.; Morimoto, M.; Tomita, F. *Biochem. Biophys. Res. Commun.* **1986**, *135*, 397.

(8) Sarstedt, B.; Winterfeldt, E. *Heterocycles* **1983**, *20*, 469.

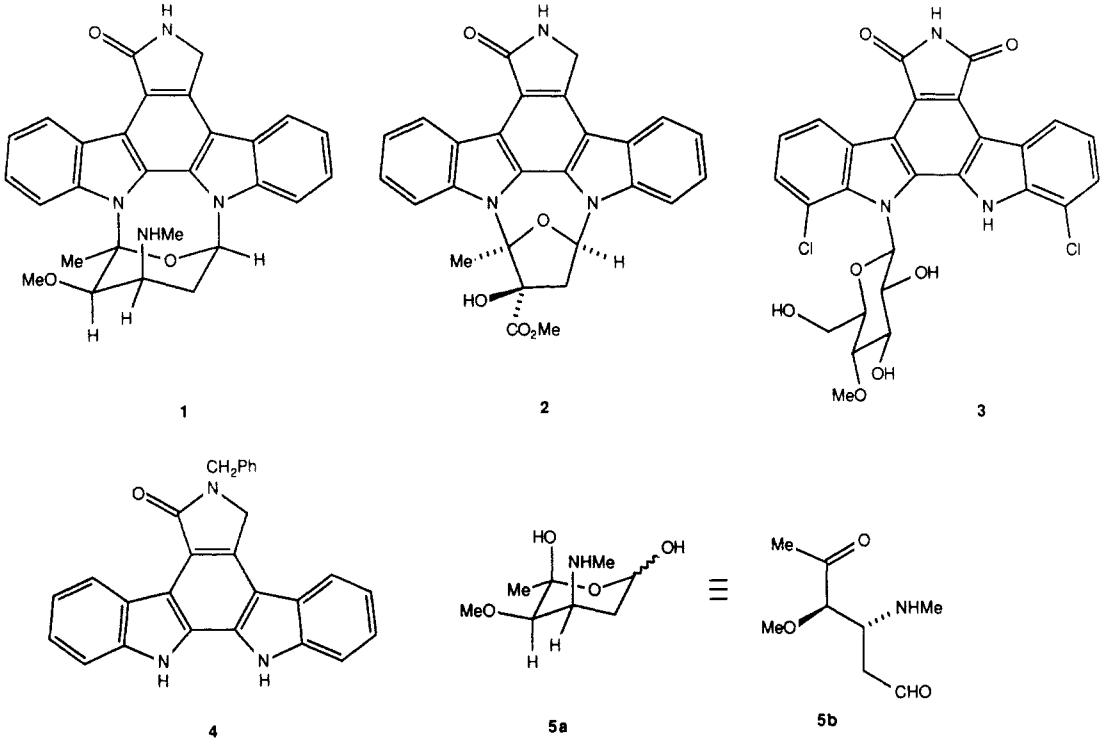
(9) Hughes, I.; Raphael, R. A. *Tetrahedron Lett.* **1983**, *24*, 1441.

(10) Magnus, P.; Sear, N. *Tetrahedron* **1984**, *40*, 2795.

(11) For our previous applications of this cycloaddition, see: (a) Garigipati, R. S.; Morton, J. A.; Weinreb, S. M. *Tetrahedron Lett.* **1983**, *24*, 987. (b) Garigipati, R. S.; Freyer, A. J.; Whittle, R. R.; Weinreb, S. M. *J. Am. Chem. Soc.* **1984**, *106*, 7861. (c) Natsugari, H.; Whittle, R. R.; Weinreb, S. M. *J. Am. Chem. Soc.* **1984**, *106*, 7867. (d) Remiszewski, S. W.; Whittle, R. R.; Weinreb, S. M. *J. Org. Chem.* **1984**, *49*, 3243. (e) Remiszewski, S. W.; Stouch, T. R.; Weibreb, S. M. *Tetrahedron* **1985**, *41*, 1173. (f) Garigipati, R. S.; Cordova, R.; Parvez, M.; Weinreb, S. M. *Tetrahedron* **1986**, *42*, 2979. (g) Remiszewski, S. W.; Yang, J.; Weinreb, S. M. *Tetrahedron Lett.* **1986**, *27*, 1853.

(12) We are grateful to Professor Raphael for providing the details of this reduction.

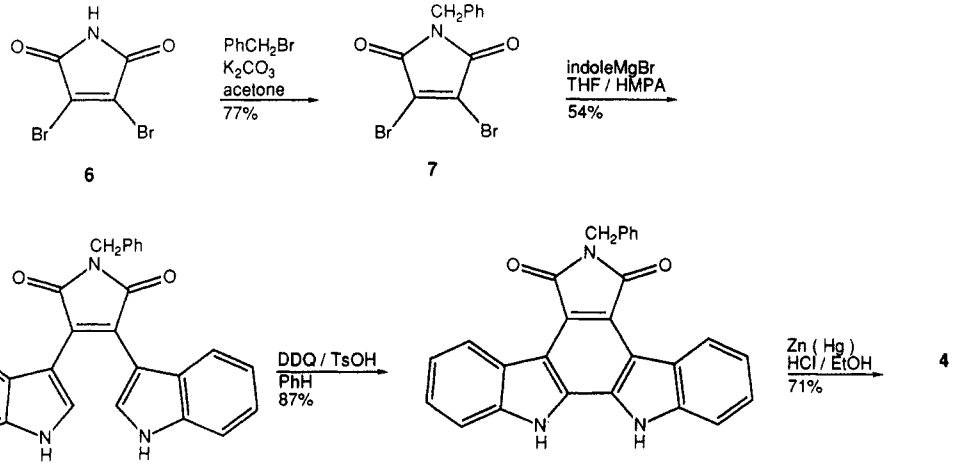
0022-3263/87/1952-1177$01.50/0



1 2 3

4 5a 5b

Scheme I



6 7 8 9

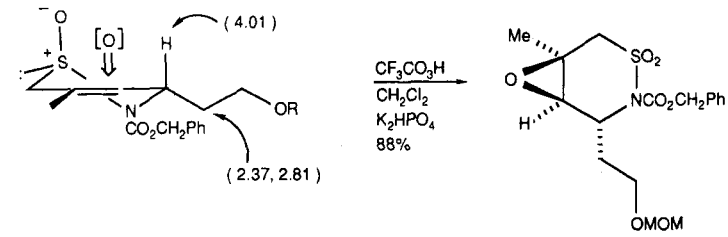
of deoxyamino sugars.[11d,e] The work described here on synthesis of the staurosporine aminohexoses **5a**/**5b** utilizes some novel transformation chemistry of the heterocyclic products of this type of Diels–Alder reaction.

The dienes used in the [4 + 2] cycloadditions were prepared efficiently as shown in Scheme II. Readily available diene ester **10**[13] was deprotonated with LDA to give an extended enolate, which on quenching with acetic acid afforded deconjugated diene ester **11**.[14] Reduction of **11** with lithium aluminum hydride yielded diene alcohol **12** (97%), which could be protected as the methoxymethyl ether **13**[15] and the *tert*-butyldimethylsilyl ether **14**.[16]

Cycloadditions of both of these dienes with benzyl sulfinylcarbamate[11b] proceeded in a completely regioselective manner in high yields in toluene at room temperature. Diene **13** afforded a chromatographically separable 2:1 mixture of epimeric 3,6-dihydrothiazine oxides **15** and **16**, respectively. Similarly, diene **14** gave a 2.2:1 mixture of adducts **17** and **18**. These additions are in accord with the known orientational preferences of *N*-sulfinyl Diels–Alder reactions.[17] No other regioisomers were detected in either series.

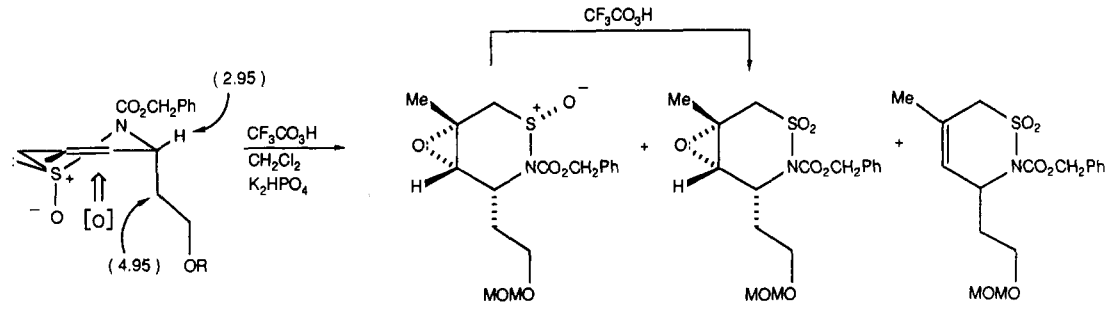
The relative stereochemistry of **17** and **18** could be established by ^{1}H NMR europium-induced shift experiments. Our recent work[11b-d] and that of others[18] has demonstrated that 3,6-dihydrothiazine oxides prefer to exist in conformations having the sulfur–oxygen bond quasi-axial. Thus, **17** and **18** probably have the solution conformations shown in **17a** and **18a**, respectively. As-

(13) Boyd, J.; Epstein, W.; Frater, G *J. Chem. Soc., Chem. Commun.* **1976**, 380.
(14) Cf. Stevens, R. V.; Cherpeck, R. E.; Harrison, B. L.; Lai, J.; Lapalme, R. *J. Am. Chem. Soc.* **1976**, *98*, 6317.
(15) Stork, G.; Takahashi, T. *J. Am. Chem. Soc.* **1977**, *99*, 1275.
(16) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(17) For reviews of this cycloaddition, see: (a) Kresze, G.; Wucherpfennig, W. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 149. (b) Weinreb, S. M.; Staib, R. R. *Tetrahedron* **1982**, *23*, 3087. (c) Bussas, R.; Kresze, G.; Munsterer, H.; Schwobel, A. *Sulfur Rep.* **1983**, *2*, 215.
(18) Hanson, P.; Stockburn, W. A. *J. Chem. Soc., Perkin Trans. 2* **1985**, 589. See also: Mock, W. L.; Nugent, R. M. *J. Am. Chem. Soc.* **1975**, *97*, 6521.



15a R = MOM
17a R = TBS

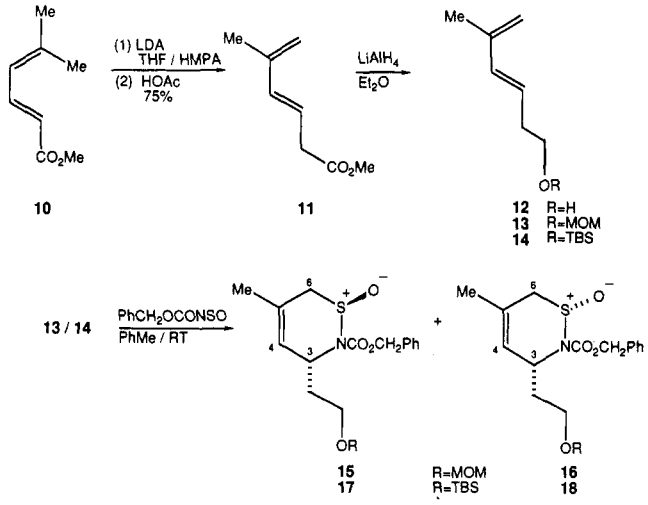
19



16a R = MOM
18a R = TBS

20 (18%) **21** (51%) **22** (24%)

Scheme II



10 **11** **12** R=H **13** R=MOM **14** R=TBS

15 **17** **16** **18**

suming that europium complexation occurs with the polar axial sulfinyl oxygen, the relative ^1H NMR induced shifts, which are shown in parentheses in the structures, are in line with the assigned stereochemistry of **17** (trans) and **18** (cis). Similar shift reagent experiments on MOM derivatives **15a** and **16a** were not conclusive due to competing complexation sites.

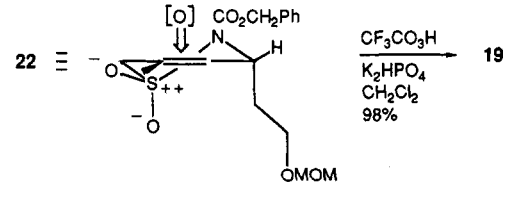
We next turned to experiments intended to introduce an oxygen with β-stereochemistry at C-4 of the Diels–Alder adducts. Thus, the major isomer in the MOM-protected series **15** was treated with buffered trifluoroperacetic acid[19] to give *exclusively* the desired β-epoxy sultam **19**. The stereochemistry of this compound was establshed by subsequent transformations (vide infra).

Epoxidation of the minor cis adduct **16** under the same conditions took a totally different and rather unexpected stereochemical course. In this case, the reaction was more complex, giving a mixture of α-epoxide **20**, α-epoxy sultam **21**, and some unepoxidized sultam **22**. Further oxidation of **20** at sulfur gave sultam **21**, indicating that both compounds were in the same α-epoxide stereochemical series. *None of the β-epoxide was detected in this oxidation.*

We believe these results are best rationalized by a mechanism involving a syn epoxidation directed by the sulfinyl oxygen. Diels–Alder adduct **15** probably exists in conformation **15a**[11b] having a quasi-axial, polar oxygen–sulfur bond. This oxygen can hydrogen-bond to the trifluoroperacetic acid, promoting syn delivery to give the β-epoxide. Subsequent oxidation at sulfur would afford sultam **19**. A related syn-directing effect was recently observed with this highly acidic peracid in olefinic systems having allylic oxygen substituents that do not bear a proton.[20,21]

The minor Diels–Alder adduct **16** would be expected to exist as conformer **16a**.[11b] A syn epoxidation here involving the quasi-axial sulfinyl oxygen would lead to the observed α-epoxides. The quasi-axial side chain in **16a** may provide enough steric hindrance that the epoxidation reaction is slow relative to **15**, and thus some sultam **22** is formed.

We could also show that sultam **22** is *not* an intermediate in the epoxidation of minor dihydrothiazine oxide **16**. Treatment of **22** with trifluoroperacetic acid under similar conditions gave *only* β-epoxide **19**. Since the β-series of epoxides is needed for the staurosporine aminohexose, this proved a useful observation (vide infra). The stereoselectivity of this epoxidation can be explained if one assumes that sultam **22** has conformation **22a**. A quasi-



22a

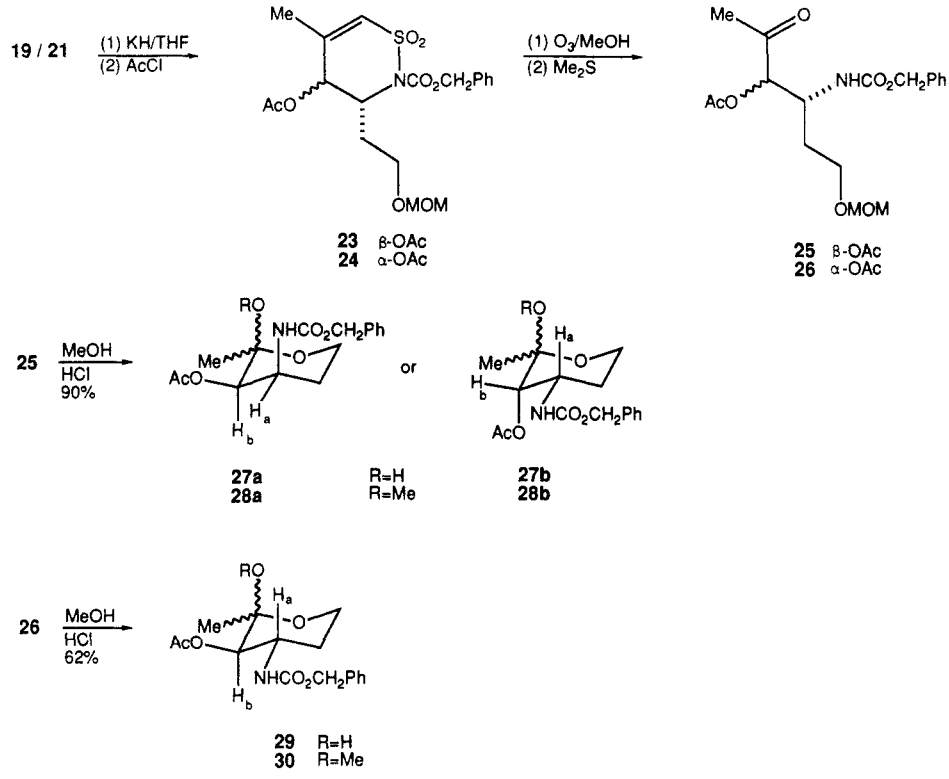
axial side chain should be favorable in order to avoid $A^{1,3}$ strain.[22] Epoxidation of **22** is most likely controlled by

(19) Emmons, W. D.; Pagano, A. S. *J. Am. Chem. Soc.* **1955**, *77*, 89.

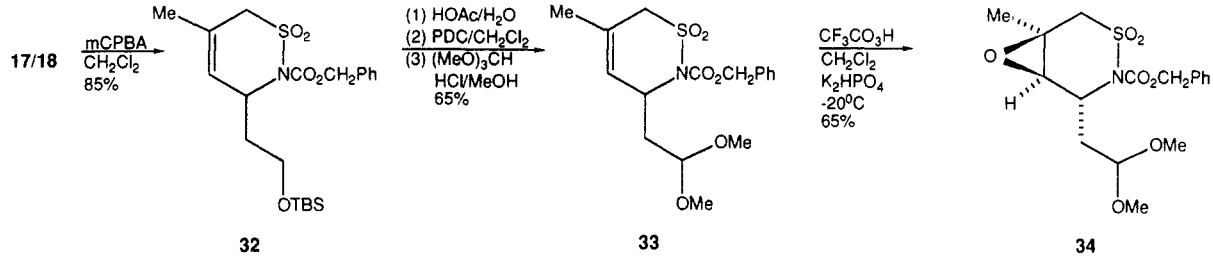
(20) For a review of directed epoxidations, see: Berti, G. *Top. Stereochem.* **1973**, *7*, 93.

(21) McKittrick, B. A.; Ganem, B. *Tetrahedron Lett.* **1985**, *26*, 4895. See also: Johnson, M. R.; Kishi, Y. *Tetrahedron Lett.* **1979**, 4347.

Scheme III



Scheme IV



steric factors, since the less polar sultam oxygens are probably not capable of effectively hydrogen-bonding to the peracid. Thus, oxidant approach from the least congested face of **22a** would afford the observed β-epoxide.

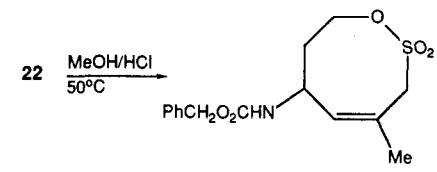
In order to prove the relative configurations of **19** and **21**, and to test the projected route to the staurosporine amino sugar, the transformations shown in Scheme III were effected. Treatment of β-epoxy sultam **19** with potassium hydride, followed by acetylation of the resulting alkoxide, gave the unsaturated sultam **23** (64%). Ozonolysis of this compound yielded methyl ketone **25** (60%). A similar series of reactions on α-epoxy sultam **21** gave acetate **24**, which could be ozonized in poor yield to ketone **26**.

The MOM protecting group of **25** was removed with hot methanolic HCl to give a mixture of a hemiketal, formulated as either **27a** or **27b**, and a methyl glycoside (either **28a** or **28b**). Although it was not possible to assign configuration to the anomeric centers of these cyclization products, both clearly had H_a/H_b in a cis-axial/equatorial relationship (J = 3.1 Hz), as required for the staurosporine monosaccharide (cf. pyranose **5a**). Similarly, deprotection of epimeric ketone **26** gave a mixture of hemiketal **29** and methyl glycoside **30** (anomeric configuration again not established) which showed a trans-diaxial H_a/H_b relationship (J = 10.7 Hz).

(22) Johnson, F. *Chem. Rev.* **1968**, *68*, 375.

The problem of obtaining the undesired α-epoxide from one of the epimeric Diels–Alder adducts could be easily solved by first oxidizing the cycloadduct mixture **15/16** to the sultam **22** with *m*-chloroperbenzoic acid. This reagent does not produce any epoxidation products. Further treatment of **22** with trifluoroperacetic acid as described above gives solely the desired β-epoxide **19** in excellent yield.

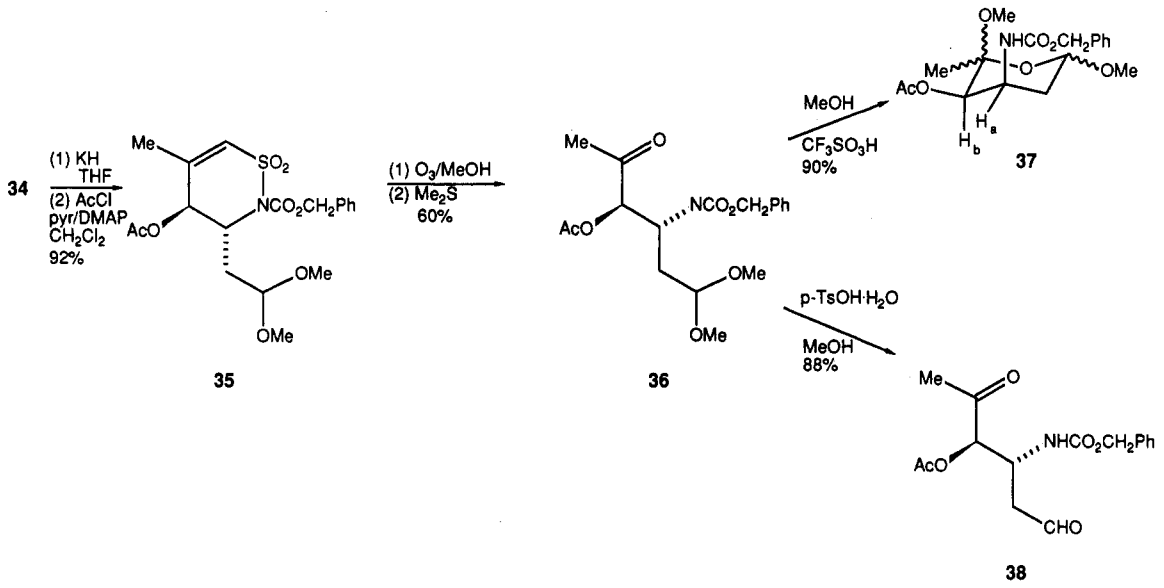
In order to prepare aminohexose derivatives such as **5**, it was necessary to adjust the oxidation level of the terminal side-chain carbon of sultam **22** to that of an aldehyde. Therefore, MOM-protected compound **22** was treated with methanolic HCl in an attempt to produce the corresponding primary alcohol. However, only the interesting rearranged eight-membered ring cyclic sulfonate **31** was formed (70% yield).



31

To avoid this problem, we turned to the mixture of TBS-protected Diels–Alder adducts **17/18**, which was oxidized to sultam **32** with *m*-chloroperbenzoic acid

Scheme V

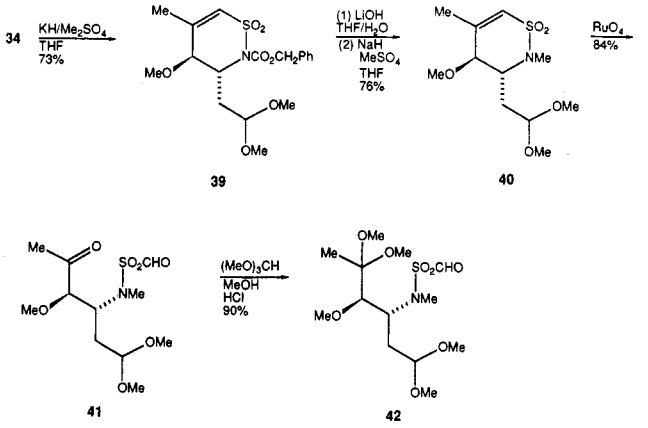


(Scheme IV). Mild acidic hydrolysis of the silyl ether group of **32** afforded the sensitive primary alcohol, which was immediately oxidized to the corresponding aldehyde with pyridinium dichromate[23] and was protected as the dimethyl acetal **33**. As anticipated, trifluoroperacetic acid oxidation of **33** gave the β-epoxide **34** stereospecifically.

The transformations of epoxide **34** to derivatives of the staurosporine sugar **5** paralleled those shown in Scheme III. Therefore, **34** was converted to acetate **35** (Scheme V), which upon ozonolysis afforded methyl ketone **36**. This compound could be cyclized to a pyranose similar to **5a** by treatment with triflic acid in anhydrous methanol, affording dimethyl glycoside **37** as a single isomer. ^{1}H NMR analysis of **37** showed a cis relationship of the acetoxy and carbamate groups (J_{ab} = 3.1 Hz), but the configuration of the anomeric centers is unknown. If methyl ketone **36** was treated with strong methanolic acid in the presence of a trace of water, only the keto aldehyde **38** was formed.

Since the staurosporine sugar has *O*- and N-methyl substituents, the series of compounds shown in Scheme VI was also prepared. Epoxide **34** was opened with potassium hydride, and the resulting alkoxide was *O*-methylated in situ to yield ether **39**. The benzyl carbamate group of **39** was removed hydrolytically, and the resulting sultam was N-methylated to produce **40**. Despite considerable effort, compound **40** could not be ozonized to the desired methyl ketone. In general, only intractable tars were formed. Because this transformation could not be affected, and since ozonolyses of several other related unsaturated sultams had tended to be rather capricious, we investigated alternative double-bond cleavages. The best procedure eventually discovered for the desired conversion utilized ruthenium tetraoxide, generated in situ from ruthenium dioxide and sodium metaperiodate.[24] Using this method, **40** was oxidized to methyl ketone **41** in good yield. Interestingly, this compound bears a formyl sulfonamide functionality, an array that is essentially unknown. We intend to further explore the chemistry of this functional group in the future. Ketone **41** could be cleanly converted to acetal ketal **42** under acidic conditions that maintained this formyl sulfonamide moiety.

Scheme VI



In order to eventually develop a total synthesis of staurosporine (**1**) from the individual components, it will be necessary to solve several important problems. First, one must develop methodology to generate the bis-N-glycosidic bonds between the aromatic unit and an aminohexose moiety. In addition, nontrivial regiochemical and stereochemical considerations must be addressed. We hope to investigate these problems in future research.

Experimental Section

3,4-Dibromo-2,5-dihydro-1-(phenylmethyl)-1*H*-pyrrole-2,5-dione (7). To a solution of 670 mg (2.63 mmol) of 3,4-dibromomaleimide (**6**) in 10 mL of acetone were added 387 mg of anhydrous potassium carbonate and 0.33 mL (470 mg, 2.8 mmol) of benzyl bromide. The reaction mixture was stirred at room temperature overnight. Water was added and the mixture was extracted with ethyl acetate. The organic extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was passed through a short column of silica gel, eluting with ethyl acetate, and the product was purified by sublimation (0.03 Torr/85 °C), yielding 702 mg (77%) of the *N*-benzylmaleimide **7**. A sample of **7** was recrystallized from ethyl acetate: mp 117–117.5 °C: IR (KBr) 1780, 1720, 1600 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 4.70 (2 H, s), 7.30 (5 H, s); MS, *m/z* (relative intensity) 347 (41), 345 (100), 343 (43), 319 (4), 317 (9), 315 (4), 266 (42), 464 (41), 238 (32), 236 (32), 91 (85).

3,4-Dihydro-3,4-di-1*H*-indol-3-yl-1-(phenylmethyl)-1*H*-pyrrole-2,5-dione (8). To a solution of 2.0 mL (6.0 mmol) of ethereal 3.0 M phenylmagnesium bromide in 32 mL of dry ether was added dropwise over 10 min a solution of 714 mg (6.1 mmol)

(23) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, *399*.
(24) Carlsen, P.; Katsuki, T.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

of indole in 16 mL of dry benzene, and the resulting solution was refluxed for 2 h.

The solution of the Grignard reagent was cooled to −10 °C and 0.05 mL of HMPA was added, followed by dropwise addition of a solution of 984 mg (2.9 mmol) of dibromomaleimide **7** in 16 mL of dry benzene. The dark violet solution was refluxed for 44 h. The reaction mixture was cooled and 10 mL of saturated NH_4Cl solution was added. The mixture was extracted with ethyl acetate. The organic extract was washed with water, brine, and dried (Na_2SO_4). The solvent was removed in vacuo, afforded a dark red solid residue, which was purified by recrystallization from acetone/H_2O, giving 650 mg (54%) of product **8**: mp 286–287 °C; IR (KBr) 3400, 1755, 1685, 1615, 1520 cm^{-1}; ^1H NMR (360 MHz, Me_2CO-d_6) δ 4.85 (2 H, s), 6.63 (1 H, dd, J = 8.2, 7.0 Hz), 6.63 (1 H, dd, J = 8.2, 7.0 Hz), 6.93 (2 H, br d, J = 7.9 Hz), 6.99 (1 H, dd, J = 7.9, 7.0 Hz), 6.99 (1 H, dd, J = 8.2, 7.0 Hz), 7.27 (1 H, m), 7.35 (2 H, m), 7.41 (2 H, br d, J = 8.2 Hz), 7.44 (2 H,m), 7.90 (2 H, m), 10.89 (2 H, br s); ^{13}C NMR (50 MHz, Me_2CO-d_6) δ 172.5, 138.7, 137.2, 130.0, 129.9, 129.4,128.8,128.4, 126.8, 122.8, 122.4, 120.4, 112.4, 112.3, 107.6, 107.5, 42.4; MS, m/z (relative intensity) 417 (100), 256 (75), 91 (24); UV (MeOH) λ_{max} (log ϵ) 466 (3.91), 374 (3.78), 285 (sh, 4.12), 277 (4.17). Anal. Calcd for $C_{27}H_{19}N_3O_2$: C, 77.68; H, 4.59; N, 10.07. Found: C, 77.70; H, 4.63; N, 9.90.

12,13-Dihydro-6-(phenylmethyl)-5*H*-indolo[2,3-*a*]carbazole-5,7(6*H*)-dione (9). A solution of 43.8 mg (0.150 mmol) of diindolylmaleimide **8**, 37.2 mg (0.164 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, and a catalytic amount of *p*-toluenesulfonic acid in 25 mL of dry benzene was refluxed for 0.5 h under nitrogen. The benzene was removed in vacuo and the residue was dissolved in ethyl acetate. The organic phase was washed with saturated $NaHSO_3$, brine, and dried (Na_2SO_4). The solvent was removed in vacuo and the yellow solid residue was purified by preparative TLC, eluting with ethyl acetate/hexane (2:1), yielding 37.8 mg (87%) of **9** as a fluorescent yellow solid. A sample of **9** was recrystallized from ethyl acetate: mp 308–309 °C dec; IR (KBr) 3350, 1740, 1690 cm^{-1}; ^1H NMR (200 MHz, Me_2CO-d_6) δ 5.00 (2 H, s), 7.31–7.72 (13 H, m), 9.15 (2 H, d, J = 8.3 Hz), 11.32 (2 H, br s); MS, m/z (relative intensity) 415 (100), 282 (24), 254 (24), 91 (23); UV (MeOH) λ_{max} (log ϵ) 402 (3.71), 316 (4.75), 305 (sh, 4.58), 283 (4.58), 277 (sh, 4.39), 235 (4.71); exact mass calcd for $C_{27}H_{17}N_3O_2$ 415.1321, found 415.1322.

Methyl 5-Methyl-3,5-hexadienoate (11). To a solution of diisopropylamine (9.25 g, 0.092 mol) in 250 mL of dry THF at −35 °C was added 59.0 mL of 1.55 M *n*-butyllithium in hexane. After stirring the mixture for 15 min, 17.4 mL of HMPA was added dropwise over 5 min. After an additional 30 min, a solution of diene ester **10**[13] (11.7 g, 0.083 mol) in 40 mL of THF was added over 45 min, and the mixture was stirred for 4 h. The dark red solution was poured into a rapidly stirred solution of 150 mL of 10% acetic acid/H_2O. The mixture was extracted with hexane, and the organic extracts were combined, washed with H_2O and brine, and dried ($MgSO_4$). The oily residue was distilled [78 °C (18 Torr)] to yield the deconjugated ester **11** (8.74 g, 75%): ^1H NMR (200 MHz, $CDCl_3$) δ 1.86 (3 H, s), 3.15 (2 H, d, J = 7.2 Hz), 3.70 (3 H, s), 4.93 (2 H, s), 5.73 (1 H, m), 6.23 (1 H, d, J = 15.6 Hz); IR (film) 3000–2900, 1740, 1605, 1440, 1250, 1200, 1160, 970, 880 cm^{-1}; MS, m/z (relative intensity) 140 (10), 125 (17), 114 (39), 98 (43), 83 (100), 55 (70).

5-Methyl-3,5-hexadienol (12). Diene ester **11** (7.78 g, 0.55 mol) in 50 mL of ether was added dropwise to a suspension of lithium aluminum hydride (2.11 g, 0.056 mol) at a rate that maintained a gentle reflux. After 1 h, the excess hydride was destroyed by the careful dropwise addition of 2 mL of H_2O, followed by the addition of 4 mL of 15% aqueous NaOH and 2 mL of H_2O. The resulting slurry was stirred for 10 min and was filtered. The solution was dried ($MgSO_4$), and the solvent was removed in vacuo to give diene alcohol **12** as an oil (6.0 g, 97%), which was used without further purification: ^1H NMR (200 MHz, $CDCl_3$) δ 1.84 (3 H, t, J = 1.2 Hz), 2.30 (1 H, br s), 2.37 (2 H, m), 3.67 (2 H, t, J = 6.7 Hz), 4.91 (2 H, br s), 5.63 (1 H, dt, J = 15.5, 6.7 Hz), 6.24 (1 H, br d, J = 15.5 Hz); IR (film) 3350, 3000–2940, 1605, 1440, 1380, 1050, 960 cm^{-1}; MS, m/z (relative intensity) 112 (80), 99 (26), 81 (100), 67 (76), 53 (43), 41 (81), 28 (35).

(*E*)-6-(Methoxymethoxy)-2-methyl-1,3-hexadiene (13). To a solution of 1.63 g (12.9 mmol) of diene alcohol **12** in 10 mL of methylene chloride and 5 mL of diisopropylethylamine at 0 °C was added 2.2 mL of chloromethyl methyl ether.[15] The reaction mixture was gradually warmed to room tempeature and was stirred overnight. The excess chloromethyl methyl ether was removed in vacuo in an efficient fume hood. The residue was diluted with 30 mL of 5% HCl and ether. The organic layer was washed with a saturated $NaHCO_3$ solution, water, and brine and dried ($MgSO_4$). Concentration of the organic layer in vacuo afforded a liquid residue that upon bulb-to-bulb distillation yielded 1.63 g (81%) of methoxymethyl ether **13**: bp 80 °C (4.5 Torr); IR (film) 3095, 1680, 1610, 1040, 970, 890 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.84 (3 H, br s), 2.42 (2 H, m), 3.35 (3 H, s), 3.62 (2 H, t, J = 7 Hz), 4.63 (2 H, s), 4.90 (2 H, br s), 5.67 (1 H, dt, J = 15, 7 Hz), 6.27 (1 H, br d, J = 15 Hz).

(*E*)-6-(*tert*-Butyldimethylsiloxy)-2-methyl-1,3-hexadiene (14). To a solution of diene alcohol **12** (6.0 g, 0.054 mol) in 24 mL of DMF at 0 °C was added *tert*-butyldimethylchlorosilane (9.67 g, 0.064 mol) in one portion, followed by imidazole (9.18 g, 0.135 mol).[16] After 16 h, the reaction mixture was poured into 100 mL of H_2O and was extracted with ethyl acetate. The organic phase was washed with H_2O and brine and dried (Na_2SO_4). Concentration of the organic layer in vacuo afforded a residue that was purified by flash chromatography, eluting with 10% ethyl acetate/hexane, to yield the silyl ether **14** as an oil (12.0 g, 97%): ^1H NMR (200 MHz, $CDCl_3$) δ 0.06 (6 H, s), 0.91 (9 H, s), 1.83 (3 H, t, J = 1.0 Hz), 2.34 (2 H, dd, J = 6.9, 3.7 Hz), 3.77 (2 H, t, J = 6.7 Hz), 4.88 (2 H, s), 5.68 (1 H, m), 6.16 (1 H, d, J = 5.7 Hz); IR (film) 2975, 2960, 2925, 1600, 1460, 1380, 1250, 1100, 950, 815, 770 cm^{-1}; MS, m/z (relative intensity) 226 (4), 169 (100), 141 (11), 127 (49), 115 (15), 101 (6), 89 (25), 75 (55), 73 (56), 59 (11), 41 (5), 28 (16).

Preparation of 3,6-Dihydrothiazine Oxides 15/16 and 17/18. To a solution of 1.40 g (7.1 mmol) of benzyl sulfinylcarbamate[11b] in 20 mL of dry toluene at room temperature was added a solution of 0.802 g (5.14 mmol) of MOM-protected diene **13** in 10 mL of dry toluene. The reaction mixture was stirred at room temperature for 3 h. The solvent was removed in vacuo, water was added to the residue, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine and dried (Na_2SO_4). The solvent was removed in vacuo, and the adducts were separated by flash chromatography on silica gel, eluting with ethyl acetate/hexane (2:3).

The less polar compound (553 mg, 30%) was the cis adduct **16**: IR (film) 1720, 1380, 1295, 1040 cm^{-1}; ^1H NMR (360 MHZ, $CDCl_3$) δ 1.88 (3 H, d, J = 1.2 Hz), 2.09 (1 H, m), 2.21 (1 H, m), 3.23 (1 H, d, J = 16.5 Hz), 3.35 (3 H, s), 3.43 (1 H, dd, J = 16.5, 1.2 Hz), 3.62 (2 H, m), 4.59 (2 H, s), 5.24 (1 H, d, J = 12.2 Hz), 5.27 (1 H, d, J = 12.2 Hz), 5.87 (1 H, br s) , 7.38 (5 H, m); ^{13}C NMR (25 MHz, $CDCl_3$) δ 169.1, 147.2, 139.2, 139.0, 138.6, 131.4, 129.6, 100.3, 67.0, 62.2, 50.8, 47.7, 46.2, 28.2, 14.0; CIMS, m/z 354 (M^+ + 1), 322.

The more polar compound (1.12 g, 61%) was the trans adduct **15**: IR (film) 1720, 1380, 1290, 1100, 1040 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.78 (1 H, m), 1.97 (3 H, s), 2.20 (1 H, m), 3.33 (3 H, s), 3.34 (1 H, dd, J = 15.0, 1.2 Hz), 3.48 (1 H, dq, J = 15.0, 1.2 Hz), 3.55 (2 H, t, J = 6.0 Hz), 4.56 (2 H, s), 4.71 (1 H, m), 5.25 (1 H, d, J = 12.2 Hz), 5.32 (1 H, d, J = 12.1 Hz), 6.11 (1 H, m), 7.37 (5 H, m); CIMS, m/z 354 (M^+ + 1), 322, 220.

3,6-Dihydrothiazine oxides **17** and **18** were prepared by the above procedure from 4.38 g of diene silyl ether **14** and 4.2 g of benzyl sulfinylcarbamate[11b] and were separated by flash chromatography (30% ethyl acetate/hexane).

The less polar isomer (2.45 g, 30%) was the cis adduct **18**: ^1H NMR (200 MHz, $CDCl_3$) δ 0.01 (6 H, s), 0.85 (9 H, s), 1.80 (3 H, s), 2.01 (2 H, m), 3.16 (1 H, m), 3.37 (1 H, m), 4.66 (1 H, t, J = 1.6 Hz), 5.21 (2 H, s), 5.82 (1 H, t, J = 1.6 Hz), 7.29 (5 H, m); IR (film) 3060, 3040, 2955, 2940, 2895, 2860, 1720, 1500, 1460, 1380, 1295,1260, 1100, 840, 780, 700 cm^{-1}; MS, m/z (relative intensity) 423 (0.3), 408 (0.2), 360 (13), 322 (0.3), 283 (0.4), 169 (6), 91 (100), 73 (14), 59 (3), 41 (3).

The more polar isomer (5.50 g, 67%) was the trans adduct **17**: ^1H NMR (200 MHz, $CDCl_3$) δ 0.01 (6 H, s), 0.85 (9 H, s), 1.73 (1 H, m), 1.97 (3 H, s), 2.10 (1 H, m), 3.39 (2 H, m), 3.64 (2 H, t, J = 6.1 Hz), 4.69 (1 H, m), 5.28 (2 H, dd, J = 12.3, 16.8 Hz), 6.08–6.74 (1 H, m), 7.37 (5 H, m); IR (film) 3060, 3040, 2960, 2940, 2900, 2860, 1720, 1500, 1475, 1380, 1290, 1250, 1100, 835, 775, 700 cm^{-1};

MS, m/z (relative intensity) 423 (3), 326 (89), 316 (5), 284 (1), 270 (1), 185 (1), 169 (5), 91 (95), 73 (15), 59 (4), 41 (1).

Phenylmethyl (1α,5α,6α)-5-[2-(Methoxymethoxy)ethyl]-1-methyl-7-oxa-3-thia-4-azabicyclo[4.1.0]heptane-4-carboxylate 3,3-Dioxide (19). Method A. To a solution of 280.8 mg (0.760 mmol) of sultam **22** in 15 mL of methylene chloride at 0 °C containing a suspension of 1.0 g of anhydrous K_2HPO_4 was added 2.8 mL of a freshly prepared solution of trifluoroperacetic acid[19] in methylene chloride. The reaction mixture was gradually warmed to room temperature over a period of 1 h. The inorganic salts were removed by filtration, and the filtrate was concentrated in vacuo. The β-epoxy sultam **19** (188 mg, 64%) was purified by flash chromatography, eluting with ethyl acetate/hexane (1:1): IR (film) 1730, 1280, 1160 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.51 (3 H, s), 2.15 (1 H, m), 2.43 (1 H, m), 3.00 (1 H, s), 3.30 (3 H, s), 3.32 (1 H, d, J = 15.0 Hz), 3.65 (2 H, m), 3.66 (1 H, d, J = 15.0 Hz), 4.52 (2 H, s), 5.19 (1 H, ddd, J = 8.9, 6.3, 0.9 Hz), 5.24 (2 H, s), 7.37 (5 H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 153.2, 134.6, 128.6, 128.5, 127.9, 96.6, 69.5, 64.4, 58.3, 57.8, 57.6, 55.3, 52.5, 32.2, 24.3; CIMS, m/z 386 (M^+ + 1), 354, 310, 220.

Method B. To a solution of 833.7 mg (2.36 mmol) of trans Diels–Alder adduct **15** in 20 mL of methylene chloride containing 4.1 g of anhydrous K_2HPO_4 at −10 °C was added 4.4 mL of a freshly prepared solution of trifluoroperacetic acid in methylene chloride.[19] The reaction mixture was vigorously stirred at −10 °C for 30 min. The inorganic salts were removed by filtration and the filtrate was concentrated in vacuo. Purification of the residue by flash chromatography on silica gel, eluting with ethyl acetate/hexane (1:1), affording 800 mg (88%) of β-epoxide **19** identical with material prepared by method A.

Preparation of Sultam 22, α-Epoxide 20, and α-Epoxy Sultam 21. To a solution of 254.8 mg (0.721 mmol) of cis Diels–Alder adduct **16** in 7 mL of methylene chloride at −10 °C containing 1.63 g of anhydrous K_2HPO_4 was added dropwise a freshly prepared solution of trifluoroperacetic acid[19] in methylene chloride until TLC indicated that the starting material had been consumed. The inorganic salts were removed by filtration, and the filtrate was concentrated in vacuo. The crude material was separated into three components by preparative TLC using ethyl acetate/hexane (1:1) as eluant. The least polar compound (143 mg, 51%) was α-epoxy sultam **21**: mp 52–55 °C; IR (film) 1730, 1280, 1160 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.48 (3 H, s), 2.25 (2 H, m), 3.27 (1 H, d, J = 4.3 Hz), 3.49 (1 H, d, J = 15.0 Hz), 3.64 (2 H, m), 3.67 (1 H, d, J = 15.0 Hz), 4.56 (2 H, s), 5.15 (1 H, td, J = 7.6, 4.3 Hz), 5.27 (2 H, s), 7.37 (5 H, m); ^{13}C NMR (50 mHz, $CDCl_3$) δ 152.7, 134.7, 128.5, 128.1, 96.5, 69.6, 58.3, 57.6, 55.5, 55.4, 53.3, 31.7, 22.6; CIMS, m/z 386 (M^+ + 1), 354, 310, 220.

The middle band contained 65 mg (24%) of the sultam **22**.

The most polar compound (49 mg, 18%) was the α-epoxide **20**: IR (film) 1720, 1385, 1280, 1110, 1040 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.48 (3 H, s), 2.29 (2 H, m), 3.13 (1 H, d, J = 15.0 Hz), 3.36 (3 H, s), 3.38 (1 H, d, J = 15.0 Hz), 3.49 (1 H, d J = 4.9 Hz), 3.70 (2 H, m), 4.62 (2 H, s), 4.96 (1 H, m), 5.20 (1 H, d, J = 12.2 Hz), 5.28 (1 H, d, J = 12.2 Hz), 7.37 (5 H, s); CIMS, m/z 370 (M^+ + 1), 338.

Preparation of Sultams 22 and 32 from Diels–Alder Adducts. A solution of m-chloroperbenzoic acid (2.73 g, 0.016 mol) in 50 mL of CH_2Cl_2 was added dropwise to a mixture of cycloadducts **17** and **18** (6.68 g, 0.016 mol) and 12 g of $NaHCO_3$ in 125 mL of CH_2Cl_2. After 10 h, the reaction mixture was poured into 100 mL of H_2O and was extracted with CH_2Cl_2. The combined organic extract was washed with saturated sodium bisulfite solution, saturated sodium bicarbonate solution, and brine and dried ($MgSO_4$). The solvent was removed in vacuo, and the residue was purified by flash chromatography, eluting with 25% ethyl acetate/hexane, to afford sultam **32** (6.0 g, 85%): ^1H NMR (200 MHz, $CDCl_3$) δ 0.01 (6 H, s), 0.85 (9 H, s), 2.05 (3 H, m), 3.49 (1 H, d, J = 16.5 Hz), 3.65 (2 H, t, J = 6 Hz), 3.82 (1 H, dd, J = 16.5, 0.8 Hz), 5.21 (1 H, m), 5.25 (2 H, s), 5.66 (1 H, dd, J = 0.6, 0.9 Hz), 7.40 (5 H, m); IR (film) 2980, 2960, 2920, 1720, 1450, 1380, 1360, 1295, 1260, 1160, 1140, 1095, 840, 790, 700 cm^{-1}; CIMS, m/z 440 (M^+ + 1), 439, 395, 376.

Sultam **22** could be prepared in a similar manner from the mixture of epimeric adducts **15** and **16** in 98% yield after flash chromatography [ethyl acetate/hexane (2:3)]: mp 65–75 °C; IR (film) 1730, 1390, 1370, 1300, 1265, 1175, 1040 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.82 (3 H, s), 2.04 (1 H, m), 2.26 (1 H, m), 3.33 (3 H, s), 3.53 (1 H, d, J = 16.5 Hz), 3.60 (2 H, m), 3.87 (1 H, dd, J = 16.5, 0.9 Hz), 4.53 (2 H, s), 5.25 (1 H, m), 5.28 (2 H, s), 5.64 (1 H, br s), 7.38 (5 H, m).

Phenylmethyl *trans*-4-(Acetyloxy)-3,4-dihydro-3-[2-(methoxymethoxy)ethyl]-5-methyl-2*H*-1,2-thiazine-2-carboxylate 1,1-Dioxide (23). To a solution of 138 mg (0.359 mmol) of β-epoxy sultam **19** in 10 mL of dry THF was added 10 drops of 35% KH dispersion in mineral oil, and after 30 min 0.1 mL of distilled acetyl chloride was added. The reaction mixture was stirred at room temperature for 23 h and was diluted with saturated NH_4Cl solution. The reaction mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried (Na_2SO_4). The solvent was removed in vacuo and the residue was purified by preparative TLC, eluting twice with ethyl acetate/hexane (1:1), producing 98 mg (64%) of *trans*-acetoxy sultam **23**: IR (film) 1750, 1710, 1340, 1270, 1230 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 2.02 (3 H, d, J = 1.5 Hz), 2.08 (2 H, m), 2.57 (3 H, s), 3.35 (3 H, s), 3.58 (2 H, m), 4.58 (1 H, d, J = 6.7 Hz), 4.61 (1 H, d, J = 6.7 Hz), 5.10 (1 H, d, J = 2.1 Hz), 5.18 (1 H, d, J = 11.9 Hz), 5.23 (1 H, d, J = 11.9 Hz), 5.52 (1 H, ddd, J = 9.0, 6.9, 2.1 Hz), 6.36 (1 H, q, J = 1.5 Hz), 7.38 (5 H, s); CIMS, m/z 428 (M^+ + 1), 396, 354, 306, 202.

Phenylmethyl *cis*-4-(Acetyloxy)-3,4-dihydro-3-[2-(methoxymethoxy)ethyl]-5-methyl-2*H*-1,2-thiazine-2-carboxylate 1,1-Dioxide (24). To a solution of 68.5 mg (0.178 mmol) of α-epoxy sultam **21** in 10 mL of dry THF was added 5 drops of 35% KH dispersion in mineral oil, and the mixture was stirred for 1.5 h, at which time 0.1 mL of acetyl chloride was added. The reaction mixture was stirred at room temperature for 30 h and was diluted with 3 mL of saturated NH_4Cl solution. The mixture was extracted with ethyl acetate, which was washed with water and brine and dried (Na_2SO_4). The solvent was removed in vacuo, and the residue was purified by preparative TLC, eluting with ethyl acetate/hexane (1:1), affording 24.5 mg (32%) of *cis*-acetoxy sultam **24**: IR (film) 1760, 1715, 1335, 1240 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.93 (3 H, p, J = 1.2 Hz), 2.08 (1 H, m), 2.24 (1 H, m), 2.56 (3 H, s), 3.31 (3 H, s), 3.47 (1 H, m), 3.59 (1 H, m), 4.52 (1 H, d, J = 6.4 Hz), 4.56 (1 H, d, J = 6.4 Hz), 5.23 (2 H, s), 5.49 (1 H, ddd, J = 7.6, 5.2, 3.7 Hz), 5.60 (1 H, br, d, J = 5.2 Hz), 6.20 (1 H, br s), 7.40 (5 H, m); CIMS, m/z 428 (M^+ + 1), 396, 354.

Phenylmethyl (*R,*R**)-[2-(Acetyloxy)-1-[2-(methoxymethoxy)ethyl]-3-oxobutyl]carbamate (25).** A mixture of ozone/oxygen was passed through a solution of 43.5 mg (0.102 mmol) of the unsaturated sultam **23** in 10 mL of methanol at −20 °C. After 2 h, the reaction mixture was purged of ozone with nitrogen. An excess of dimethyl sulfide was added at −20 °C and the reaction mixture was gradually warmed to room temperature. The excess dimethyl sulfide and solvent were removed in vacuo. The residue was purified by preparative TLC, eluting with ethyl acetate, producing 22.2 mg (60%) of methyl ketone **25**: IR (film) 3300 (br), 1755, 1730, 1660, 1260 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.75 (2 H, m), 1.97 (3 H, s), 2.27 (3 H, s), 3.33 (3 H, s), 3.54 (2 H, m), 4.56 (1 H, d, J = 6.7 Hz), 4.58 (1 H, d, J = 6.7 Hz), 4.67 (1 H, m), 5.14 (1 H, d, J = 3.7), 5.19 (2 H, s), 5.86 (1 H, br d, J = 8.6 Hz), 7.39 (5 H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 202.4 169.9, 154.4, 134.7, 128.8, 128.7, 128.5, 96.5, 83.1, 70.4, 64.0, 55.3, 46.7, 29.2, 26.7, 23.3; CIMS, m/z 368 (M^+ + 1), 346, 306, 216.

Phenylmethyl (*R,*S**)-[2-(Acetyloxy)-1-[2-(methoxymethoxy)ethyl]-3-oxobutyl]carbamate (26).** A mixture of ozone/oxygen was bubbled through a solution of 60.5 mg (0.142 mmol) of cis-unsaturated sultam **24** in 10 mL of methanol at −15 °C for 2 h. Excess ozone was purged from the reaction mixture with oxygen, and the solvent was removed in vacuo. The residue was dissolved in methylene chloride and cooled to room temperature, and the solvent was removed in vacuo. The crude product was purified by preparative TLC, eluting with ethyl acetate/hexane (2:1), affording 7.0 mg (17% based on recovered starting material) of ketone **26**: ^1H NMR (360 MHz, $CDCl_3$) δ 1.90 (2 H, m), 1.92 (3 H, s), 2.27 (3 H, s), 3.35 (3 H, s), 3.58 (2 H, t, J = 5.8 Hz), 4.58 (1 H, d, J = 6.7 Hz), 4.61 (1 H, d, J = 6.7 Hz), 4.90 (1 H, m), 5.08 (1 H, d, J = 2.1 Hz), 5.19 (2 H, s), 5.68 (1 H, br d, J = 9.8 Hz), 7.39 (5 H, m).

Preparation of Cyclic Hemiketal 27 and Methyl Glycoside 28. A solution of 20.0 mg (0.54 mmol) of methoxymethyl ether

25 in 2 mL of methanol containing 1 drop of concentrated HCl was stirred at 50 °C for 2 h. The solvent was removed in vacuo, and two products were isolated by preparative TLC utilizing ethyl acetate as eluant. The less polar band contained 6.7 mg (37%) of the methyl glycoside **28**: IR (film) 3300, 1750, 1650, 1385, 1260 cm^{-1}; ^1H NMR (200 MHz, Me_2CO-d_6) δ 1.16 (3 H, s), 1.48 (1 H, m), 1.74 (1 H, m), 1.78 (3 H, s), 3.22 (3 H, s), 3.68 (2 H, m), 4.50 (1 H, m), 4.80 (1 H, d, J = 3.1 Hz), 5.19 (2 H, s), 7.11 (1 H, br s), 7.41 (5 H, m); MS, m/z (relative intensity) 337 (0.1), 306 (2), 263 (16), 128 (58), 91 (100); exact mass calcd for $C_{17}H_{23}NO_6$ 337.1525, found 337.1554.

The more polar band yielded 9.2 mg (3%) of the cyclic hemiketal **27**: IR (film) 3400, 3300, 1750, 1650, 1260 cm^{-1}; ^1H NMR (200 MHz, Me_2CO-d_6) δ 1.27 (3 H, s), 1.45 (1 H, m), 1.74 (1 H, m), 1.79 (3 H, s), 3.60 (1 H, ddd, J = 11.6, 5.2, 1.5 Hz), 4.01 (1 H, ddd, J = 12.8, 11.6, 3.1 Hz), 4.85 (1 H, d, J = 3.1 Hz), 5.15 (1 H, d, J = 12.5 Hz), 5.22 (1 H, d, J = 12.5 Hz), 7.12 (1 H, br d, J = 8.2 Hz), 7.40 (5 H, m); CIMS, m/z 324 (M^+ + 1).

Preparation of Cyclic Hemiketal 29 and Methyl Glycoside 30. A solution of 6.0 mg (0.016 mmol) of methoxymethyl ether **26** in 3 mL of methanol containing 1 drop of concentrated HCl was stirred at 50 °C for 2.5 h. The solvent was removed in vacuo, and two compounds were separated by preparative TLC, eluting with ethyl acetate. The less polar compound (2.1 mg, 39%) was methyl ketal **30**: IR (film) 3300, 1750, 1660, 1385, 1260 cm^{-1}; ^1H NMR (200 MHz, benzene-d_6) δ 1.18 (1 H, m), 1.24 (3 H, s), 1.42 (3 H, s), 1.81 (1 H, m), 2.88 (3 H, s), 3.23 (2 H, m), 4.45 (1 H, d, J = 10.7 Hz), 4.76 (1 H, m), 4.82 (1 H, d, J = 12.2 Hz), 4.97 (1 H, d, J = 12.2 Hz), 5.13 (1 H, br d, J = 8.6 Hz), 7.11 (5 H, m); MS, m/z (relative intensity) 337 (0.3), 307 (0.1), 263 (20), 247 (6), 91 (100); exact mass calcd for $C_{17}H_{23}NO_6$ 337.1525, found: 337.1513.

The compound of greater polarity (1.2 mg, 23%) was cyclic hemiketal **29**: IR (film) 3400, 3300, 1750, 1660, 1265 cm^{-1}; ^1H NMR (200 MHz, benzene-d_6) δ 1.18 (1 H, m), 1.30 (3 H, s), 1.39 (3 H, s), 1.70 (1 H, m), 3.26 (1 H, dd, J = 11.6, 5.2 Hz), 3.82 (1 H, br t, J = 13.1 Hz), 4.49 (1 H, d, J = 11.0 Hz), 4.74 (1 H, m), 4.82 (1 H, d, J = 12.2 Hz), 4.97 (1 H, d, J = 12.2 Hz), 5.05 (1 H, br d, J = 7.9 Hz), 7.05 (5 H, m); CIMS, m/z 324 (M^+ + 1), 306, 216, 172.

Preparation of Cyclic Sulfonate 31. A solution of sultam **22** (96 mg, 0.26 mmol) and 1 drop of concentrated HCl in 15 mL of methanol was heated at 50 °C for 4 h. The mixture was cooled and was diluted with ethyl acetate. The solution was washed with saturated sodium bicarbonate solution and brine and dried (Na_2SO_4). The solvent was removed in vacuo, and the residue was purified by preparative TLC, eluting with ethyl acetate/hexane (1:1), to yield sulfonate **31** as a colorless oil (58 mg, 70%): ^1H NMR (360 MHz, $CDCl_3$) δ 1.81 (3 H, s), 2.04 (2 H, m), 3.52 (2 H, m), 4.19 (1 H, br s), 4.31 (3 H, m), 5.16 (2 H, s), 5.55 (1 H, s), 7.39 (5 H, s); IR (film) 3250, 3050, 2925, 2850, 1745, 1450, 1400, 1280, 1140, 790 cm^{-1}; MS, m/z (relative intensity) 325 (0.2), 261 (0.5), 237 (1), 236 (9), 234 (7), 184 (1), 172 (14), 146 (23), 109 (8), 108 (14), 92 (13), 91 (100), 82 (21), 79 (10).

Preparation of Acetal 33. To a solution of sultam **32** (3.63 g, 0.0083 mol) in 15 mL of THF was added 45 mL of a 2:1 mixture of acetic acid/H_2O. After 4 h, the solvent was removed in vacuo, and the residue was dissolved in ethyl acetate. The solution was washed with saturated sodium bicarbonate solution and brine and dried (Na_2SO_4). Removal of the solvent in vacuo furnished an unstable alcohol that was used without purification.

A solution of this alcohol (2.68 g, 0.0083 mol) in 50 mL of CH_2Cl_2 was added dropwise to a stirred suspension of pyridinium dichromate (3.88 g, 0.010 mol) in 100 mL of CH_2Cl_2.[23] After 36 h, the reaction mixture was diluted with 100 mL of ether and was filtered through a short Florisil column, eluting with ether/CH_2Cl_2 (1:1). The filtrate was dried ($MgSO_4$) and concentrated in vacuo to furnish the aldehyde, which was used without further purification.

To the above aldehyde (2.65 g, 0.0082 mol) in 10 mL of CH_2Cl_2 and 40 mL of trimethyl orthoformate was added 20 mL of dry saturated methanolic HCl. After 24 h, the solution was diluted with 300 mL of ethyl acetate. The solution was washed with H_2O, saturated sodium bicarbonate solution, and brine and dried ($MgSO_4$). The solvent was removed in vacuo, and the residue was purified by flash chromatography, eluting with 30% ethyl acetate/hexane, to yield oily acetal **33** (1.97 g, 65% from **32**): ^1H NMR (200 MHz, $CDCl_3$) δ 1.81 (3 H, s), 2.04 (1 H, m), 2.33 (1 H, m), 3.26 (3 H, s), 3.27 (3 H, s), 3.51 (1 H, m), 3.86 (1 H, m), 4.44 (1 H, t, J = 4.5 Hz), 5.19 (1 H, t, J = 1.9 Hz), 5.28 (2 H, s), 5.59 (1 H, m), 7.39 (5 H, m); IR (film) 3060, 3030, 2950, 2840, 1723, 1500, 1450, 1360, 1260, 1160, 1050, 800, 750, 700 cm^{-1}; CIMS, m/z 338 (M^+ - OMe), 280, 236.

Epoxidation of Sultam 33. To a solution of 1 mL of aqueous 90% H_2O_2 in 5 mL of dry CH_2Cl_2 at 0 °C was added 5 mL of trifluoroacetic anhydride over 5 min. After standing for 20 min, the peracid solution was added in two portions over 5 min to a rapidly stirred mixture of sultam **33** (458 mg, 1.24 mmol) and 10 g of anhydrous potassium phosphate (dibasic) in 50 mL of CH_2Cl_2 at −20 °C. After 1 h, the reaction mixture was poured into H_2O and was extracted with CH_2Cl_2. The organic extract was washed with saturated sodium bicarbonate solution and brine and dried ($MgSO_4$). The solvent was removed in vacuo, and the residue was purified by radial TLC, eluting with 30% ethyl acetate/hexane, to furnish epoxide **34** (310 mg, 65%): ^1H NMR (200 MHz, $CDCl_3$) δ 1.51 (3 H, s), 2.08–2.33 (1 H,m), 2.47 (1 H, m), 3.03 (1 H, s), 3.29 (3 H, s), 3.32 (3 H, s), 3.67 (1 H, d, J = 14.1 Hz), 4.50 (1 H, m), 5.16 (1 H, m), 5.25 (2 H, s), 7.39 (5 H, m); IR (film) 3040, 3025, 2980, 2940, 2840, 1735, 1500, 1450, 1385, 1270, 1205, 1160, 1060, 812, 805, 755, 745, 700 cm^{-1}; MS, m/z (relative intensity) 385 (0.2), 353 (4), 304 (0.1), 291 (1), 279 (0.2), 250(2),217 (5), 160 (3), 113 (5), 91 (76), 75 (100), 65 (5), 55 (6).

Preparation of Acetate 35. To a solution of epoxide **34** (64 mg, 0.167 mmol) in 2 mL of THF at 0 °C was added sodium hydride (16 mg of a 50% mineral oil dispersion). The mixture was warmed to room temperature and was stirred for 1 h. The reaction mixture was diluted with H_2O and was extracted three times with ethyl acetate. The extracts were combined, washed with brine, and dried ($MgSO_4$). The solvent was removed in vacuo to yield the allylic alcohol, which was dissolved in a mixture of 2 mL of CH_2Cl_2 and 2 mL of pyridine. To this mixture was added 0.1 mL of acetic anhydride and 2 crystals of 4-(dimethylamino)pyridine. After 12 h, the reaction mixture was poured into H_2O and was extracted with CH_2Cl_2. The extract was washed with saturated ammonium chloride solution, saturated sodium bicarbonate solution, and brine and dried ($MgSO_4$). The solvents were removed in vacuo, and the residue was purified by flash chromatography, eluting with 40% ethyl acetate/hexane, to yield the allylic acetate **35** as an oil (60 mg, 92%): ^1H NMR (200 MHz, $CDCl_3$) δ 2.01 (3 H, d, J = 1.3 Hz), 2.04–2.31 (2 H, m), 2.56 (3 H, s), 3.34 (3 H, s), 3.36 (3 H, s), 4.46 (1 H, dd, J = 3.8, 6.7 Hz), 5.12 (1 H, d, J = 2.2 Hz), 5.20 (2 H, d, J = 2.2 Hz), 5.49 (1 H, dt, J = 2.1, 7.7 Hz), 6.36 (1 H, d, J = 1.4 Hz), 7.35 (5 H, m); IR (film) 3030, 2975, 2915, 1750, 1705, 1440, 1360, 1330, 1265, 1230, 1140, 1060, 950, 850, 785, 755, 740, 700 cm^{-1}; CIMS, m/z 396 (M^+ - OMe), 292, 244, 202.

Ozonolysis of Allylic Acetate 35. A stream of ozone/oxygen was passed through a solution of allylic acetate **35** (85 mg, 0.199 mmol) in 15 mL of dry methanol at −35 °C. After 2 h, the reaction mixture was flushed with nitrogen, 3 mL of dimethyl sulfide was added, and the solution was warmed to room temperature. The excess dimethyl sulfide and the solvent were removed in vacuo. The residue was dissolved in ethyl acetate, washed with H_2O and brine, dried (Na_2SO_4), and evaporated. The crude product was purified by preparative TLC, eluting with ethyl acetate, to yield methyl ketone **36** as an oil (44 mg, 60%): ^1H NMR (200 MHz, $CDCl_3$) δ 1.67–1.85 (2 H, m), 1.97 (3 H, s), 2.27 (3 H, s), 3.28 (3 H, s), 3.29 (3 H, s), 4.43 (1 H, m), 4.62 (1 H, dd, J = 3.7, 8.1 Hz), 5.17 (1 H, d, J = 3.5 Hz), 5.2 (2 H, s), 5.99 (1 H, br d, J = 8.0 Hz), 7.39 (5 H, s); IR (film) 3600–3200, 3060, 2940,2850, 1755, 1730, 1660, 1540, 1440, 1380, 1260, 1040, 960, 785, 750, 700 cm^{-1}.

Formation of Dimethyl Glycoside 37. To a solution of methyl ketone **36** (8.7 mg, 0.024 mmol) in anhydrous methanol (1 mL) was added 2 drops of trifluoromethanesulfonic acid, and after 48 h the reaction mixture was diluted with ethyl acetate. The solution was washed with H_2O, saturated sodium bicarbonate solution, and brine and dried ($MgSO_4$). The organic phase was concentrated in vacuo, and the residue was purified by flash chromatography, eluting with 7% methanol/$CHCl_3$, to yield dimethyl glycoside **37** (7.8 mg, 90%): ^1H NMR (200 MHz, $CDCl_3$) δ 1.31 (3 H, s), 1.85 (3 H, s), 3.30 (3 H, s), 4.60 (1 H, m), 4.65 (1 H, ddd, J = 3.1, 6.5, 12.2 Hz), 4.73 (1 H,, d, J = 3.1 Hz), 5.08 (2

H, s), 5.32 (1 H, br d, J = 7.3 Hz), 7.38 (5 H, s); IR (film) 3300 3060, 2950, 2840, 1750, 1650, 1540, 1450, 1380, 1260, 1180, 1130, 1050, 1000, 960, 900, 790, 760, 700 cm^{-1}; MS, m/z (relative intensity) 367 (2), 366 (7), 336 (2), 293 (2), 260 (1), 235 (3), 159 (11), 131 (25), 91 (100), 75 (36), 58 (11).

Preparation of Keto Aldehyde 38. A solution of methyl ketone **36** (17 mg, 0.41 mmol) and *p*-toluenesulfonic acid monohydrate in 5 mL of methanol was stirred at room temperature for 5 h. The solvent was removed in vacuo, and the residue was purified by preparative TLC, eluting with ethyl acetate, to yield keto aldehyde **38** as a colorless oil (13 mg, 88%): ^1H NMR (200 MHz, $CDCl_3$) δ 1.97 (3 H, s), 2.29 (3 H, s), 2.70 (2 H, d, J = 5.4 Hz), 4.94 (1 H, m), 5.06 (1 H, d, J = 3.9 Hz), 5.19 (2 H, s), 6.09 (2 H, d, J = 8.5 Hz), 7.43 (5 H, s), 9.67 (1 H, s); IR (film) 3300, 3050, 2920, 1750, 1725, 1650, 1540, 1380, 1260, 1120, 1050, 950, 780, 750 cm^{-1}; MS, m/z (relative intensity) 321 (3), 293 (0.5), 144 (4), 126 (10), 114 (18), 98 (9), 91 (100), 86 (5), 79 (4), 72 (30), 60 (9), 43 (29).

Formation of Methyl Ether 39. To a stirred solution of epoxide **34** (210 mg, 0.546 mmol), dimethyl sulfate (0.5 mL, 5.12 mmol), and 0.5 mL of HMPA in 5 mL of THF was added potassium hydride (ca. 100 mg of a 25% mineral oil dispersion). After 90 min, 1 mL of triethylamine was added, and the mixture was stirred for an additional 30 min. The mixture was cooled to 0 °C, and the excess potassium hydride was destroyed carefully with H_2O. The reaction mixture was extracted with ether. The organic phase was washed with saturated ammonium chloride solution, saturated sodium bicarbonate solution, and brine and dried ($MgSO_4$). The solution was concentrated in vacuo, and the residue was purified by flash chromatography, eluting with 30% ethyl acetate/hexane, to yield methyl ether **39** (158 mg, 73%): ^1H NMR (200 MHz, $CDCl_3$) δ 1.86 (3 H, t, J = 1.3 Hz, 1.98 (2 H, m), 2.86 (3 H, s), 3.39 (3 H, s), 3.40 (3 H, s), 4.53 (1 H, m), 4.55 (1 H, dd, J = 3.6, 7.6 Hz), 5.26 (1 H, d, J = 7.0 Hz), 5.21 (2 H, s), 6.38 (1 H, t, J = 1.3 Hz), 7.38 (5 H, s); IR (film) 3040, 2950, 2840, 1750, 1635, 1450, 1385, 1335, 1250, 1170, 1125, 1060, 960, 905, 795, 750, 740, 700 cm^{-1}; CIMS, m/z 400 (M^+ + 1), 399, 384, 368.

Preparation of *N*-Methyl Sultam 40. A mixture of carbamate **39** (150 mg, 0.37 mmol) and 42 mg of $LiOH \cdot H_2O$ in 5 mL of THF/H_2O (85:15) was stirred for 2 h. The reaction mixture was poured into H_2O and extracted three times with ethyl acetate. The combined organic extracted was washed with saturated ammonium chloride solution, saturated sodium bicarbonate solution, and brine and dried (Na_2SO_4). The solvent was removed in vacuo to furnish a sultam (99 mg, 99%), which was used in the next step without purification.

To a solution of the above sultam (99 mg, 0.37 mmol) and 0.1 mL of dimethyl sulfate in 3 mL of THF was added NaH (15 mg of an 80% dispersion in mineral oil). After 30 min, 0.4 mL of triethylamine was added to destroy excess dimethyl sulfate, followed by the dropwise addition of H_2O to consume excess sodium hydride. The reaction mixture was extracted with ethyl acetate. The organic extract was washed with saturated ammonium chloride solution, saturated sodium bicarbonate solution, and brine and dried (Na_2SO_4). The solution was concentrated in vacuo, and the residue was purified by flash chromatography, eluting with ethyl acetate/hexane (1:1), to furnish *N*-methyl sultam **40** (103 mg, 76%): ^1H NMR (200 MHz, $CDCl_3$) δ 1.95 (3 H, s), 1.91–2.05 (2 H, m), 2.83 (3 H, s), 3.39 (3 H, s), 3.41 (3 H, s), 3.46 (3 H, s), 3.61 (1 H, d, J = 5.3 Hz), 4.14 (1 H, m), 4.57 (1 H, t, J = 1.4 Hz), 6.35 (1 H, m); IR (film) 2940, 2840, 1625, 1440, 1330, 1160, 1120, 1080, 960, 900, 850, 720, 640 cm^{-1}; CIMS, m/z 280 (M^+ + 1), 279, 249, 200.

Oxidation of Sultam 40 to Methyl Ketone 41. A solution of *N*-methyl sultam **40** (29 mg, 0.010 mmol) in 1 mL of CCl_4 and 1 mL of acetonitrile was added to a solution of 1 crystal of ruthenium dioxide monohydrate and sodium metaperiodate (89 mg, 0.415 mmol) in 1.5 mL of H_2O.[24] The biphasic reaction mixture was rapidly stirred for 15 min and was extracted three times with CH_2Cl_2. The organic extract was dried ($MgSO_4$), and the solvent was removed in vacuo. The oily residue was purified by flash chromatography, eluting with ethyl acetate, to yield methyl ketone **41** (27 mg, 84%): ^1H NMR (200 MHz, benzene-d_6) δ 1.68–1.92 (4 H, m), 2.06 (3 H, s), 2.21 (3 H, s), 2.75 (3 H, s), 2.83 (3 H, s), 2.97 (3 H, s), 3.02 (3 H, s), 3.07 (3 H, s), 3.15 (3 H, s), 3.27 (2 H, t, J = 2.2 Hz), 3.74 (1 H, m), 4.09–4.25 (1 H, m), 4.26 (1 H, m), 4.96 (1 H, m), 8.00 (1 H, s), 8.07 (1 H, s); IR (film) 2930, 2850, 1715, 1675, 1450, 1395, 1360, 1190, 1130, 1080, 960 cm^{-1}; CIMS, m/z 322, 304, 290, 289.

Conversion of Methyl Ketone 41 to Acetal Ketal 42. To a solution of methyl ketone **41** (4.7 mg, 0.0152 mol) in 0.5 mL of dry methanol and 0.5 mL of trimethyl orthoformate was added 1 drop of acetyl chloride. After 60 h, the reaction mixture was diluted with ethyl acetate. The solution was washed with saturated sodium bicarbonate solution and brine and dried ($MgSO_4$). The solvent was removed in vacuo, and the residue was purified by flash chromatography, eluting with 5% methanol/$CHCl_3$, to yield acetal ketal **42** (5 mg, 90%): ^1H NMR (200 MHz, $CDCl_3$) δ 1.28 (3 H, s), 1.95 (2 H, dd, J = 5.9, 9.1 Hz), 2.84 (3 H, s), 3.18 (3 H, s), 3.22 (3 H, s), 3.26 (1 H, m), 3.31 (6 H, s), 3.50 (3 H, s), 3.84 (1 H, m), 4.19 (1 H, m), 8.05 (1 H, s); IR (film) 3050, 2940, 2840,1675, 1450, 1380, 1260, 1180, 1120, 1050, 960, 875, 740 cm^{-1}; CIMS, m/z 295, 279, 247.

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